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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/021,121	12/06/2001	Ingrid W. Caras	GENENT.046DV1	3508

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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,121	CARAS, INGRID W.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *35 and 40-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35 and 40-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

The Examiner prosecuting your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Shulamith H. Shafer, Art Unit 1647.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 November 2005 has been entered.

Claims 35, and 40-49 are pending and under examination. Claim 40 has been amended, and the amendment has been made of record.

Objections

Drawings:

The drawings/figures are objected to because tables and sequence listings included in the specification must not be duplicated in the drawings. Specifically, Figures 1 and 2 disclose sequences which should be identified by SEQ ID NO:'s in the specification. See 37 C.F.R. §1.58(a) and §1.83. Appropriate correction is required.

Rejections Maintained

Claims 35, 40-49 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement; the claims contain subject matter which was not described on the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is maintained for reasons of record in the previous Office Actions of 26 May 2004 and 25 October 2004 and for reasons stated below.

Applicant traversed this rejection of the claims in the communication of 21 November 2005 by asserting that claims are fully enabled, such that, based on the teaching of the specification, one skilled in the art could have practice the invention at the time the invention was made, without undue experimentation.

Applicant reviews the legal standards for enablement (page 5, 2nd paragraph bridging page 6), with which the examiner takes no issue.

Claim 35, the independent claim of the instant invention, recites a method for accelerating neovascularization of a wound, comprising applying to the wound an angiogenically effective amount of a composition comprising an isolated polypeptide sequence of:

a) the amino acid sequence of SEQ ID NO:2 or 4, identified by applicant as AL-2; or
b) a soluble AL-2 derived from SEQ ID NO:2 or 4; or
c) a mammalian homolog or variant of SEQ ID NO:2 or 4 having at least 95% sequence identity with SEQ ID NO:2 or 4

Applicant asserts that SEQ ID NO:2 or 4 represent proteins now designated as ephrin-B3 and presents some details of the Eph family of receptors and their ligands. Applicant refers to attached Table 1 (page 6, paragraph 2), but the information contained in the Table cannot be considered, as this was not included in the communication of 21 November 2005. Applicant indicates that the specification, particularly page 48, line 25 bridging page 49, line 27, indicated that the polypeptides of SEQ ID NO:2 or 4 are useful in promoting or enhancing angiogenesis. Applicant's

arguments have been fully considered but are not found to be persuasive for the following reasons. The assertion that proteins of SEQ ID NO:2 or 4 are now recognized in the Art as ephrin-B3, a member of the B-class ligands of the ephrin family, is not in dispute. What is not shown in the specification, nor supported by the art at the time of the instant invention, is a nexus between ephrin-B3 and its role as a potential medicament for accelerating neovascularization of a wound. The specification only provides prophetic suggestions that polypeptides of SEQ ID NO:2 or 4 "are expected to accelerate the healing process in a broad spectrum of wound conditions" (page 49, lines 10-11); however, no evidence is presented that the methods of the present invention have accelerated the healing process in any *in vitro* or model system. Applicant asserts that the ephrin ligands are promiscuous in their interaction with Eph receptors, and have been shown to bind to multiple Eph receptors; thus, one should assume that they would initiate identical biological responses. However, this reasoning is not considered persuasive. No evidence is presented in the specification of AL-2 binding to any member of the Eph receptor family. Example 4 of the specification is a prophetic one; it presents no documentation of any Eph-related receptor activation by AL-2. The art provides no teachings to remedy the lack of guidance in the instant specification. The art recognizes the role of Ephrin-B2 in the development of the embryonic vascular system. Gale et al (2001, Dev. Biol. 230:151-160) teach that ephrin-B2 expression continues to selectively mark arteries during later embryonic development as well as in the adult (page 159, column 1, paragraph 1). The teachings of Shin et al (2001, Dev. Biol. 230:139-150) disclose that Ephrin B2 is expressed in adult arteries, microvessels and capillaries (page 142, column 2, paragraph 1, and page 140, figure 1). Huynh-Do et al (2002, J Cell Sci. 115:3073-3081) teach that an Eph-B1 fusion protein can promote neovascularization in a mouse corneal micropocket assay (page 3073, abstract). The teachings of Hafner et al. (2005, World J Gastroenterol 11:4511-4518) disclose that contacting IEC-6 cells with an Eph-B1 fusion protein induces expression of wound-healing associated genes (page 4511, abstract). None of the above references teach that ephrin-B3 (herein claimed as AL-2 represented by SEQ ID NO:2 and 4) plays any role in neovascularization or wound healing.

The claims of the instant invention recite applying a composition comprising a soluble AL-2 derivative derived from SEQ ID NO:2 or 4 for accelerating neovascularization. The art teaches that ephrins cannot act as soluble mediators but must be membrane-bound to activate their receptors (see, for example, 2002, Oike et al. Blood 100:1326-1333, page 1326, column 1, 1st paragraph). Martiny-Baron et al (2004, Neoplasia 6:248-257) disclose soluble EphB4 causes a reduction of intratumoral microvessel density, indication an inhibition of angiogenesis (page 248, abstract). Thus, the skilled artisan could not predict whether a medicament comprising a soluble derivative would promote or inhibit neovascularization. Therefore, the totality of the evidence taught by the art does not support a role for Ephrin-B3 (either the mature AL-2 polypeptide or a soluble derivative) in promoting neovascularization of a wound.

Applicant argues that the specification of the present application provides ample teaching about methods for making amino acid variants of SEQ ID NO:2 or 4 and for identifying variants that are expected to work in the claimed methods. Applicant asserts that the skilled in the art is high, and therefore the skilled artisan would not have to undertake undue experimentation to prepare the variants covered by the pending claims and use them in the claimed methods (page 7, paragraph 4). Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. The level of one of ordinary skill in the art is only one of the factors to be considered in the analysis of enablement. The level of predictability in the art, the amount of direction provided by the inventor and the existence of working examples in the disclosure must also be considered. The general references in the disclosure to making modifications to the disclosed sequences of the recited polypeptides does not provide sufficient guidance to making modifications which would result in variants or muteins that would retain the biological functions of the full length, mature AL-2 molecule.

The specification does not reasonably provide enablement for a mammalian homologue protein having at least 95% sequence identity with SEQ ID NO:2 or 4. Applicant does not disclose any actual or prophetic examples of any of the possible variants or an AL-2 polypeptide. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic

effects on the protein's function. For example, Mickle et al. (2000, Med Clin North Am 84:597-607) teach that cystic fibrosis (CF) is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation, a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving rise to the CF phenotype, thus showing that even the substitution of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990, Biochemistry John Wiley and Sons Inc.) teaches that a single Glu to Val substitution in the β subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in a homozygous individual, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, Yan et al. (2000, Science 290:523-527) teach that in certain cases, a change of only two amino acid residues in a protein results in switching the binding of the protein from one receptor to another. The amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural requirements of the protein are lacking, it is unpredicatable as to which variations, if any, meet the limitations of the claims, being able to accelerate neovascularization. Applicants are required to enable one of skill in the art to make and use the claimed invention. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides which share 95% or greater sequence homology to the amino acid sequences of SEQ ID NO:2 and 4 in the methodology of the claimed invention.

The rejection of Claims 35 and 40-49 under U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record in the previous Office Actions of 26 May 2004 and 25 October 2004 and for reasons stated below. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant traverses this rejection and asserts that while only two specific sequences are disclosed in the present application, there is extensive teaching for making and using other variants and that the current claims recite certain structural and functional features. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. Adequate written description requires more than a mere statement that variants are part of the invention, and general references directed to making variants and homologues. The claims do not require that the polypeptide possess any particular conserved structure. The specification does not provide sufficient distinguishing identifying characteristics of the genus. There is no identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus, variants of Ephrin-B3 which have angiogenic or neovascularization activity.

Conclusions

No claims allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER